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Articles

Nocebo Effect in patients with Adverse Drug Reactions: The Role of Emotion Regulation

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Abstract

Patients who have experienced adverse drug reactions (ADRs) can show some psychological problems both pre-existing than consequently the reactions. Anxiety, depression, somatization, as well as a minor capability of expressing emotions, have been demonstrated in some of these subjects. Nevertheless, a negative expectation toward a new drug administration related to some nocebo reactions can complicate the evaluation of these patients. This study aims to investigate the link between the nocebo effect and emotional functioning in ADRs patients to better understanding the psychological mechanisms involved in this phenomenon. Therefore, patients who have manifested or not (non responders) a nocebo reaction following the administration of an inert substance (placebo) have been compared. One hundred twenty patients (N = 30 with nocebo reactions; N = 90 non responders) completed the *Difficulties in Emotion Regulation Scale*, *Emotion Regulation Questionnaire, and Toronto Alexithymia Scale-20*. ADRs patients with nocebo reactions showed: 1) higher level of Cognitive Reappraisal than non responders; 2) associations between higher level of emotion dysregulation and not immediate drug reactions; 3) associations between higher level of alexithymia, Expressive Suppression and more frequent access to healthcare services; 4) alexithymia and Expressive Suppression as predictors of more frequent access to healthcare services, evident in 35% of the sample. The clarification of some psychological mechanisms involved in the nocebo effect is a basic prerequisite to better understand and manage these patients.

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1. Introduction

Adverse drug reactions (ADRs) are very common in clinical practice, and women are involved in 57–70% of cases (Rademaker, 2001). These patients show various and polymorphous symptoms (e.g., cutaneous symptoms, respiratory symptoms, systemic symptoms), not infrequently associated with psychological distress (De Pasquale et al., 2012). Their clinical history is characterized by anxiety or depression, but it is unclear if psychological factors are antecedents or are the consequence of this particular kind of disease (Berrino et al., 2005).

According to Hauser and colleagues (Häuser, Hansen, & Enck, 2012), ADRs can be related to the nocebo effect that occurs when patients suffering from several illnesses exhibit troublesome symptoms after the administration of inert substances. This is an opposite phenomenon to the placebo effect (i.e., a substance without medical effects which benefits the health status because of the patient's belief that the substance is effective) (Požgain, Požgain, & Degmečić, 2014). The nocebo phenomenon is influenced by several factors, as patient's expectation, previous experience, setting, appearance of the drug, and psychological features as anxiety, depression, and a tendency toward somatization (Berrino et al., 2005; Bizzi, Voltolini, Fiaschi, & Cavanna, 2019; Hermes, Hein, & Henz, 2006; Liccardi et al., 2004; Rief, Hofmann, & Nestoriuc, 2008; Wells & Kaptchuk, 2012). In particular, depression is associated with a pessimistic perception of self or events and in the context of receiving a new drug, the expectation is that the medication is not likely to do anything positive and it will make things worse. Anxiety is linked with a hypervigilant reaction for harmful dangerous situations and may anticipate harm from a pill and the somatization (Colloca & Benedetti, 2007).

Studies on the nocebo effect mainly focus on biological mechanisms (Benedetti et al., 2007; Colloca & Miller, 2011; Lombardi, Gargioni, Canonica, & Passalacqua, 2008) rather than on psychological features as emotional functioning. However, this would have direct implications for well-being of these patients (Balzarotti, Biassoni, Prunas, & Velotti, 2016; Gross & John, 2003), considering that an inability to cope with negative emotions is considered a central feature of clinical outcome (Aldao, Nolen-Hoeksema, & Schweizer, 2010); a difficulty in regulating emotions is linked with psychosomatic symptoms (Lundh, Wikström, & Westerlund, 2001); alexithymic features are linked with psychosomatic disease as well as to a general deficit in the ability to tolerate negative emotions and to connect them to physical sensations (Subic-Wrana, Beutel, Knebel, & Lane, 2010).

Therefore, an emotion regulation perspective is adopted in the study considering emotion dysregulation, maladaptive use of emotion regulation strategies, and alexithymia features. Specifically, emotion dysregulation is defined here as a multidimensional construct encompassing maladaptive ways of responding to emotional distress, including: a lack of awareness, understanding, and acceptance of emotions; an unwillingness to experience emotional distress as part of pursuing desired goals; difficulties controlling behaviors in the face of emotional distress; and deficits in the modulation of emotional arousal through effective emotion regulation strategies (Gratz & Roemer, 2004). Expressive Suppression (the opposite to Cognitive Reappraisal) is meant here as maladaptive emotion regulation strategy that attempts to hide, reduce or inhibit emotion regulation strategies on a verbal and non-verbal level, without

reducing the subjective and physiological experience of negative emotions that continue unresolved (Gross, 1998). Alexithymia is meant as difficulties identifying feelings, communicating feelings to other people and externally oriented thinking (Bagby, Parker, &Taylor, 1994).

Reviewing the literature on multifaceted role played by emotions in ADRs patients, Patriarca and colleagues (1991) found a tendency to suppress the expression of affects using the Rorschach's test in patients with multiple drug intolerance. The presence of a smaller quantity of energy led to a minor capability of expression emotions and a major expression of depressive feelings, probably for an expressive inhibition and an impossibility to mental elaboration. Additionally, De Pasquale et al. (2012) found in these patients an inability to use verbal language to describe feelings, an impoverished fantasy life, and a poor communicative style. Alexithymia features were also found in patients with other types of allergic diseases, like bronchial asthma (Baiardini et al., 2011; Baiardini, Sicuro, Balbi, Canonica, & Braido, 2015). However, studies on emotional functioning in ADRs patients with nocebo effects are lacking.

Starting from these considerations whereby an emotional inhibition is common in patients with multiple drug intolerance (De Pasquale et al., 2012; Patriarca et al., 1991) and a general deficit to regulate emotions connecting with physical sensations may worsen the outcome of the patients (Colloca & Benedetti, 2007; Rief et al., 2008), it is hypothesized to find emotional problems mainly in ADRs patients that show nocebo reactions. In this way, two groups of subjects that in an identical diagnostic context have manifested or not (non responders) a nocebo effect administrating a placebo are compared. The first study's objective concerns to test the emotional functioning in patients with nocebo reactions comparing with non responders; secondly, the link between clinical anamnestic data (i.e., number of drug reactions, time of reactions, severity of reactions, access to healthcare services) and emotional problems in these patients is investigated to better understand the existence of factors favoring.

2. Materials and methods

2.1 Participants

Among all the patients with a clinical history of ADR, 120 were recruited consecutively from the Allergy Unit of the San Martino IST University Hospital (Genoa, Italy) in the first months of 2016 because they needed to be submitted to challenge test. The mean age of participants is 46.59 (SD = 15.50), 82% are females and 21% have awarded a degree. The anamnestic clinical data concerning the previous reactions are shown in Table 1.

Seventy-six percent of patients have a history of multiple ADR with more than one category of drugs involved and 51% have experienced immediate drug reactions. Thirty-one% of the total have experienced mild reactions, while most of them have moderate-severe reactions, and 52% referred to Emergency Health Care structures (Medical Ward or Hospital Emergency Department).

Table 1. Clinical data of patients with ADRs

Clinical data of patients	Percentages %
Number of drug reactions	1 = 24%
	>1 = 76%
Time of reactions	Immediate = 51%
	Not immediate = 30 %
	Not specified = 19%
Severity of reactions	Mild = 31%
	Moderate - Severe = 59%
	Not specified = 10%
Access to healthcare services	Yes = 52%
	No = 48%

Of the total participants, N = 30 (25%) showed nocebo reactions to oral placebo while N = 90 were non responders. The demographic characteristic of the sample is shown in Table 2. The only significant difference is about the age ($t(118) = 3.22$, $p = .002$), showing older age in patients with nocebo effect than non responders.

Table 2. Demographic characteristic of ADRs patient with nocebo effects and no responders

		Patients with nocebo effect (N = 30)	Non responders (N = 90)	Statistics
Gender	Female	28.6%	71.4%	$chi^2_{(1)} = 3.64$, $p = .057$
	Male	9.1%	90.9%	
Age mean (SD)		54.20 (12.77)	44.06 (15.56)	$t_{(118)} = 3.22$, $p = .002$**
Educational level	Non-graduates	23.4%	76.6%	$chi^2_{(1)} = .774$, $p = .379$
	Graduates	32%	68%	

Note: *** $p < .001$; ** = $p < .01$; * = $p < .05$

In almost all cases of patients with nocebo effect the reactions were mild and most of the symptoms were subjective with a few cases of objective reactions: 27% skin symptoms (itching,

burning sensation, paresthesia), 33% neurological symptoms (agitation, tremors, dizziness, headache), 20% gastrointestinal symptoms (nausea, abdominal pain, diarrhea), 10% respiratory symptoms (dyspnea, laryngeal obstruction sensation), 10% cardiovascular symptoms (hypo or hypertension, tachycardia).

2.2 Measures

The *Difficulties in Emotion Regulation Scale* (DERS; Gratz & Roemer, 2004) is a widespread self-report measure of emotion dysregulation and confirmed its good psychometric properties and its construct and predictive validity in the Italian adaptation of the scale (Giromini, Velotti, de Campora, Bonalume, & Zavattini, 2012). The DERS assesses difficulties in six clinically relevant dimensions of emotion regulation through 36 items rated on a 1 to 5 Likert (from "almost never" to "almost always"*)*. The scales were the following: No acceptance of Emotional Response (Nonacceptance), Difficulties Engaging in Goal-Directed Behavior (Goal), Impulse Control Difficulties (Impulse), Lack of Emotional Awareness (Awareness), Limited Access to Emotion Regulation Strategies (Strategies), and Lack of Emotional Clarity (Clarity). Greater scores on any of these scales are indicative of greater difficulties in each emotion regulation dimension. In our study is reported internal consistency of .93.

The *Emotion Regulation Questionnaire* (ERQ; Gross & John, 2003), a 10-item self-report questionnaire that assesses the use of an adaptive strategy of emotion regulation, the Cognitive Reappraisal (6 items), and a maladaptive strategy of emotion regulation, the Expressive Suppression (4 items). The items were rated on a 7-point-Likert scale from "strongly disagree" to "strongly agree". The Italian version of the ERQ (Balzarotti, John, & Gross, 2010) has demonstrated good internal consistency and two-month test-retest reliability (.67 for Reappraisal and .71 for Suppression), comparable to that of the original English version of the ERQ. In our study is reported internal consistency of .83 for Reappraisal and of .74 for Suppression.

The *Toronto Alexithymia Scale-20 (*TAS-20; Bagby et al., 1994) was administered in its Italian adaptation (Bressi et al., 1996) to measure individuals' levels of alexithymia. The TAS-20 is a self-report questionnaire comprising 20 items on a 5-point Likert scale. A total alexithymia score is obtained by summing scores on three dimensions: Difficulty in Identifying Feelings (DIF), Difficulty in Describing Feelings (DDF), and External Oriented Thinking (POE). In our study is reported internal consistency of .75.

2.3 Procedure

All participants voluntarily took part in the study after the first medical visit where the clinician explained the meaning of the study, providing written informed consent. After the collection of anamnestic data, including the description of symptoms and circumstances of the reaction, the patients were submitted to an allergological workup, comprehensive of oral gradual challenge test for one or more drugs. Standard procedure, beginning with a first day of placebo administration (four doses of inert substance at 30' interval, followed by one hour observation of patient) was performed by an experienced allergist together with a nurse in the hospital setting where emergency equipment was available (Bavbek, Pasaoglu, Canat, Sagduyu, & Misirligil, 2006). During the first day of the oral test, all patients compiled three questionnaires of their emotional functioning.

The oral challenge with placebo was administered according to the recommendations of the ENDA group of the European Academy of Allergy and Clinical Immunology. The psychological measures complied with the official directions established by the American Psychological Association and the Italian Association of Psychology. Since all tests were performed for diagnostic purposes, ethical committee approval was not required.

2.4 Data analytic plan

The results are analyzed using the Statistical Package for Social Science (SPSS, Version 21.0; IBM Corp., Armonk, NY, USA). Descriptive statistics are computed for all study variables and all sociodemographic information available. Parametric tests, as Independent sample t-test, Chi-square, ANOVA are used to examine group differences. Point biserial correlations are used to test the association between nominal (clinical anamnestic data of ADRs patients) and quantitative variables (DERS, ERQ, TAS-20 scores). Besides, logistic regression analysis is used to test the prediction power of emotion regulation problems on clinical anamnestic features of the ADR in nocebo patients. The level of significance for all analyses was $p < .05$.

3. Results

Table 3 shows scores derived from DERS, ERQ and TAS-20. All of these dependent variables display adequate distributional characteristics, and there is no substantial skewness or kurtosis. Comparing patients with nocebo effect (N = 30) with non responders (N = 90), the only significant difference is found on ERQ respect to Cognitive Reappraisal. Higher level of Cognitive Reappraisal in patients with nocebo effect (M = 34.20, SD = 6.89) than non

responders (M = 29.82, SD = 7.45, t(118) = 2.84, p = .005) is found. To control age differences on these scores, ANOVA is applied; findings show significant effects for age (F(1, 120) = 2.34, p = .015, eta2 = .20), but no for group (F(1, 120) = 1.41, p = .174, eta2 = .13). Significant interaction is not found.

Table 3. DERS, ERQ and TAS-20 scores in ADRs patients with nocebo effects and in non responders

Measures		**Nocebo effects**	**Non responders**	**t(118)**
		M (SD)	M (SD)	
DERS	NON ACCEPTANCE	12.27 (5.13)	12.49 (4.99)	-.21
	GOAL	13.10 (3.27)	13.29 (3.60)	-.25
	IMPULSE	11.43 (2.86)	11.61 (3.14)	-.27
	AWARENESS	23.43 (4.41)	22.67 (3.55)	.96
	STRATEGY	16.87 (5.21)	15.81 (4.01)	1.15
	CLARITY	12.80 (1.19)	13.20 (1.36)	-1.44
	DERS Total	89.90 (15.29)	89.07 (13.03)	.29
ERQ	CR	34.20 (6.89)	29.82 (7.45)	2.84*
	ES	11.77 (5.49)	11.81 (5.53)	-.04
TAS-20	DIF	13.00 (5.46)	13.29 (5.23)	-.26
	DDF	13.00 (4.50)	12.42 (3.25)	.76
	POE	27.07 (3.61)	26.82 (3.73)	.31
	TAS-20 Total	106.60 (14.43)	104.32 (14.98)	.73

Note: DERS: Difficulties in Emotion Regulation Scale; ERQ: Emotion Regulation Questionnaire; TAS-20: Toronto Alexithymia Scale-20; CR: Cognitive Reappraisal; ES: Expressive Suppression; DIF: Difficulty in Identifying Feelings; DDF: Difficulty in Describing Feelings; POE: External Oriented Thinking

Table 4 shows the correlations between clinical anamnestic data (i.e., number of drug reactions, time of reactions, severity of reactions, access to healthcare services) and emotional functioning (DERS, ERQ, and TAS-20 scores). Positive significant correlations between the time of reactions (0 = immediate, 1 = not immediate reactions) and DERS subscales (Non-Acceptance, Impulse, Strategy, DERS Total) in ADRs patients with nocebo effect are found (p values from .014 to .042). Furthermore, the access to healthcare services (0 = access, 1 = no access) is linked with Alexithymia total score (r_{pb} = -.447, p = .013) and Expressive Suppression (r_{pb} = .376, p = .040) in ADRs patients with nocebo effect. Conversely, data show a negative correlation between access to healthcare services and DERS Clarity in non responders (r_{pb} = -.213, p = .045).

None correlations between the severity of reactions (0 = mild reactions, 1 = moderate-severe reactions) or the number of drug reactions (0 = one category, 1 = more than one category of drugs involved) and emotional functioning in both groups are found.

Table 4. Point Biserial Correlations between clinical data and DERS, ERQ and TAS-20 scores in ADRs patients with nocebo effects and in no responders

	Number of drug reactions		Time of reactions		Severity of reactions		Access to healthcare services	
	Nocebo effect	Non responders	Nocebo effect	Non responders	Nocebo effect	Non responders	Nocebo effect	Non responders
NO ACCEPT.	.060	-.122	.467*	.031	.126	.106	-.079	-.143
GOAL	-.036	-.187	.219	.134	.107	.024	-.093	-.019
IMPULSE	.047	-.236	.507*	-.029	.015	.146	.201	-.104
AWAREN.	.127	.053	.114	-.083	-.095	.111	.069	-.012
STRATEGY	.101	-.136	.428*	.078	.080	.122	-.117	-.077
CLARITY	-.014	-.102	.041	-.039	.013	-.113	.057	-.213*
DERS Total	.091	-.194	.470*	.042	.069	.138	-.024	-.134
CR	.039	.123	-.097	.105	.198	.013	-.059	.177
ES	.272	-.085	-.047	-.068	-.104	.103	.376*	.054
DIF	-.155	-.085	.310	.028	.094	-.047	-.298	-.057
DDF	-.264	-.270	.093	.048	.290	.093	-316	-.148
POE	-.319	-.138	.028	-.014	.317	.117	-.244	-.189
TAS-20 Total	-.290	-.066	.293	-023	.279	.077	-.447*	-.062

Note: NON ACC.: Non acceptance; AWAREN.: Awareness; CR: Cognitive Reappraisal; ES: Expressive Suppression; DIF: Difficulty in Identifying Feelings; DDF: Difficulty in Describing Feelings; POE: External Oriented Thinking

Given the significant correlations found in patients with nocebo reactions, two separate logistic regressions have been carried out to test the prediction power of emotion regulation problems on some of the ADR clinical anamnestic features (i.e., time of reactions and access to healthcare service). The first logistic regression model (Table 5) in which time of reactions is used as a categorical variable (0 = immediate; 1 = not immediate) shows that Non-Acceptance, Impulse, Strategy, and DERS total do not significantly predict this variable. Conversely, the second logistic regression model (Table 6) in which the access of healthcare service is used as a categorical variable (0 = access; 1 = no access) shows that alexithymia (TAS-20 Total) and Expressive Suppression significantly predicted this variable. The summary model fit is significant and explains 35% of the variance.

Table 5. Logistic regression analyses in ADRs patients with nocebo effects with time of reactions as the dependent variable and emotional problems as potential predictors

Variable	B	*SE B*	Wald	*df*	*p*	95% CI
Constant	-14.73	10.38	2.01	1	.156	
Non acceptance	.34	.031	1.23	1	.267	.77, 2.58
Impulse	.59	.49	1.41	1	.234	.68, 4.75
Strategy	-.50	.59	.72	1	.396	.19, 1.93
DERS Total	.10	.17	.38	1	.539	.79, 1.55

Table 6. Logistic regression analyses in ADRs patients with nocebo effects with healthcare service access as the dependent variable and emotional problems as potential predictors

Variable	B	*SE B*	Wald	*df*	*p*	95% CI
Constant	9.46	4.69	4.06	1	.044*	
TAS-20 Total	-.12	.05	5.70	1	.017*	1.03, 1.59
ES	.24	.11	4.79	1	.029*	.81, .98

4. Discussion

The present study expands the knowledge on the psychological functioning of ADRs patients focusing on the nocebo reactions considering the paucity of studies on this topic. Starting from the assumptions whereby emotional problems are common in patients with multiple drug intolerance (De Pasquale et al., 2012; Patriarca et al., 1991) and a general deficit to regulate emotions connecting with physical sensations may worsen the outcome of the patients (Colloca & Benedetti, 2007; Rief et al., 2008), it is hypothesized to find emotional problems mainly in ADRs patients with nocebo reactions. Nevertheless, the first researchers' hypothesis is not confirmed. Conversely to Patriarca et al. (1991), findings do not confirm a higher tendency to suppress emotions in ADR patients with nocebo effects than non responders. In contrast, they differ for a higher level of Cognitive Reappraisal, an adaptive strategy that involves reconsidering a stressful situation from a different perspective, producing a positive interpretation of the situation to decrease distress (Gross, 1998). Although the effect of age is influential in this finding and could be related to more adverse reactions in older patients, emotion regulation problems cannot be considered a central feature of nocebo effects. The study of Webb (2012) can help to understand this datum.

Each emotion regulation strategy, rather than being inherently adaptive or maladaptive, can be adaptive or maladaptive in a different context or depending on different situational contingencies.

Besides, in contrast to De Pasquale et al. (2012) and other studies focused on other allergic diseases (Baiardini et al., 2011, 2015), the presence of higher difficulties identifying feelings, communicating feelings to other people and externally oriented thinking is not confirmed in this study. Nevertheless, a possible explanation of this datum is that the negative expectation of patients with ADRs may be more powerful and exceeds the conscious mind, moving beyond the emotional awareness and involving neurological markers as showed by researchers (Benedetti et al., 2007; Colloca & Miller, 2011; Lombardi et al., 2008). Finally, it is worth to note that patients analyzed by Patriarca and De Pasquale represent a particular subset of ADR patients, probably very different from the majority of patients considered in this study.

Considering the second objective on the role of emotional problems as a central feature of clinical outcome (Aldao et al., 2010; Balzarotti et al., 2016; Gross & John, 2003), a link between emotional problems and clinical anamnestic features of ADRs patients with nocebo effect has been found. More concretely, higher levels of emotion dysregulation are linked with not immediate drug reactions, while higher levels of alexithymia and Expressive Suppression are linked with more frequent access to healthcare services. This can be argued that a lack of acceptance of emotions, an inability to refrain from impulsive behavior when experiencing negative emotions, and a lack to access to emotion regulation strategies perceived as effective (Gratz & Roemer, 2004) makes the ADRs patients with nocebo effect more vulnerable to show late-onset drug reactions. Besides, the inhibition of emotion regulation strategies as well as alexithymic features makes the patients with nocebo reactions more inclined to access the healthcare service. In other words, a primitive deficit in the emotions elaboration makes the patients most needy to care (Aldao et al., 2010; Lund et al., 2001; Subic-Wrana et al., 2010), providing recurrent hospitalizations, frequent requests for medical care and increasing their health costs. This underlines that the lack of expression of emotions leads to an evolution towards illness. Conversely, the number of drugs and the severity of reactions are not linked with emotional problems. The presence of a heterogeneous sample for clinical history including both participants with non-specific and mild reactions and participants with serious allergic reactions may explain this finding.

Additionally, data from regression analyses add that if on the hand the dysregulation emotion features are not enough to predict the late-onset drug reaction, on the other hand, the inhibition of emotion regulation strategies as well as alexithymic features result as predictors of more

frequent access to healthcare services, evident in 35% of the sample. This suggests that different facets of emotional functioning have a different influence on the outcome. The knowledge of this can help the clinicians to promote a holistic comprehension of the disease (Cavanna, Bizzi, & Charpentier, 2015; Houlis, Cardinali, Cocchi, & Cavanna, 2019) and guide their behavior and reassurance communication enhancing the alliance of these patients (Planés, Villier, & Mallaret, 2016).

This study has several limitations. First, our sample size was quite small and not completely homogeneous. Studies using larger sample sizes are needed before firm conclusions can be drawn. Secondly, our study is a cross-sectional study we cannot make any causal inferences about the associations found between emotion regulation, alexithymia, and nocebo effect in ADRs patients. Thirdly, we only used self-report to evaluate emotional functioning. Future research should adopt a multi-method approach. Fourthly, an evaluation of the personality of these patients was missing, a methodological limitation that restricts the generalisability of our results.

5. Conclusion

Notwithstanding the limitations of this study, the current findings make a significant contribution to the knowledge of emotional functioning in ADRs patients with a focus on the nocebo phenomenon. Even if the role of emotions does not characterize ADRs patients with nocebo effect differently to non responders, a general deficit in the emotion regulation process connotes some of the clinical anamnestic features of these patients. Particular interesting appears to be the consequence of a dysfunctional relationship with the health services. The knowledge of this permits to better understand the nocebo phenomenon and consequently to increase insight on the management of these patients. Methods of limiting or reducing the nocebo effects must include optimal clinical-patient interactions to facilitate the emotional adjustment and promote psychological support shaping patients' expectations and enhancing the treatment alliance to limit the typical nonadherence and the treatment discontinuity of these patients (Berrino et al., 2005; Colloca & Miller, 2011; Planés et al., 2016). In this way, it is important to establish a multidisciplinary working team aimed diagnose and correctly treat these patients, including a psychological intervention (Bizzi, Sciarretta, D'Alessandro, & Picco, 2016) and encouraging professionals to support their involvement into the management of the patients (Cardinali, Migliorini, & Rania, 2019).

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